The following Listing of the Claims will replace all prior versions and all prior listings of the claims in the present application:

Listing of The Claims:

1. (Previously Amended) A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell comprising said selected antigen, wherein said cytokine of said cytokine-coated cell is exogenous to said cell, and wherein said mammal is vaccinated to said selected antigen.

2. (Previously Amended) A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine-coated cell comprises said selected antigen and is admixed with an engineered cytokine, and wherein said mammal is vaccinated to said selected antigen.

3. (Original)The method of claim 1 or claim 2 wherein said vaccine composition further comprises an opsonin-enhanced cell.

4. (Original) The method of claim 3 wherein said opsonin of said opsonin-enhanced cell is selected from the group consisting of mannose binding protein or the alpha' chain of C3b.

5. (Original) The method of any one of claims 1 or 2 wherein said cytokine of said cytokine-coated cell comprises a lipid.

6. (Original) The method of claim 5 wherein said cytokine comprises a GPI moiety.

7. (Original) The method of claim 5 wherein said cytokine comprises a fatty acid.

8. (Original) The method of claim 7 wherein said fatty acid is palmitate.

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Previously Amended) A method of vaccinating a mammal to a selected antigen, the method comprising administering to the mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine is a ligand for the GM-CSF receptor, and wherein said mammal is vaccinated to said selected antigen.

14. (Original) The method of claim 13, wherein said ligand for the GM-CSF receptor is GM-CSF.

15. (Cancelled) A method of vaccinating a mammal to a selected antigen, the method comprising; administering to a mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine is a ligand for one of the following receptors: the IL-2 receptor, the IL-4 receptor, the IL-6 receptor, the IL-10 receptor, the IL-12 receptor, the TNF-α receptor, the IFN-γ receptor, a chemokine receptor.

16. (Cancelled) The method of claim 15, wherein said ligand is selected from the group consisting of: IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, IFN-γ, or a chemokine.

17. (Currently Amended) The method of any one of claims 1, ~~9, 10,~~ or 13 ~~or 15~~, wherein said cell of said cytokine-coated cell is a pathogenic cell.

18. (Original) The method of claim 17 wherein said pathogenic cell is a malignant tumor cell.

19. (Original) The method of claim 17 wherein said cell of said pathogenic cell is selected from the group consisting of: a bacterium, a virus, a fungus, a cell of a parasite.

20. (Original) The method of claim 17, wherein said vaccine composition further comprises an opsonin-enhanced pathogenic cell.

21. (Cancelled) A method of vaccinating a mammal to a selected antigen, the method comprising administering to a mammal a vaccine composition comprising an opsonin-enhanced pathogenic cell and a cytokine-coated pathogenic cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said opsonin is selected from the group consisting of mannose binding protein or the alpha' chain of C3b.

22. (Currently Amended) The method of any one of claims 1, ~~9, 10,~~ or 13 ~~15 and 21~~, wherein said cytokine-coated cell is substantially unable to divide in vitro.

23. (Currently Amended) The method of any one of claims 1, ~~9, 10,~~ or 13 ~~15 and 21~~, wherein said vaccine composition is attenuated.

24. (Currently Amended) The method of any one of claims 1, ~~9, 10,~~ or 13 ~~15 and 21~~, wherein said cytokine is an antitumor cytokine.

25. (Currently Amended) The method of any one of claims 1, ~~9, 10,~~ or 13 ~~15 and 21~~, wherein said cytokine is extremely bioactive, natively bioactive, or suprabioactive.

REMARKS

Claims 1-8, 13-14, 17-20, and 22-25 are currently pending in the application.

Formal Matters

Sequence Listing

The Examiner notes that the specification contains amino acid sequences which are not included in the "Sequence listing" filed previously in the present application. Applicant submits that they have filed herewith a substitute sequence listing which includes the sequences indicated by the Examiner, and request that the "Sequence listing" be entered in the above captioned application.

Rejection of Claims 1-8, 13, 14, 17-20, and 22-25 Under 35 U.S.C. §112, First Paragraph

The Examiner had rejected claims under 35 U.S.C. §112, first paragraph as not being enabled for "vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine coated cell comprising said antigen". Applicant respectfully traverses this rejection.

The present invention relates to a method of vaccinating a mammal to a selected antigen comprising administering to the mammal a vaccine composition comprising a cytokine coated cell comprising the selected antigen, wherein the cytokine of the cytokine-coated cell is exogenous to the cell. The present specification defines a cytokine-coated cell as a cell modified to bear a cell surface cytokine (page 4, lines 12-13), and further defines an exogenous cytokine as a cytokine "which is introduced from or produced outside the cell" (page 10, lines 28-29). Thus the claims of the invention relate to a cytokine coated cell comprising an exogenous cytokine which is produced or introduced from outside the cell (e.g., admixed with the cell), and not expressed from the cytokine coated cell.

Applicant traverses the rejection on the grounds that the application as filed meets the enablement standard of teaching the ordinarily skilled artisan to practice the invention through the full scope of the claims.

According to prevailing authority, sufficient enablement does not require an Applicant to describe every potential embodiment encompassed by the claims, but rather requires that, after reviewing the application, the ordinarily skilled artisan be able to **reproduce** the claimed invention as claimed without resorting to "undue experimentation." In *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the Federal Circuit defined undue experimentation as a conclusion reached after weighing many factual considerations including those cited in *In re Forman*, 230 U.S.P.Q. 546 at 547 (Pat. & Trademark Off. Bd. Pat. Inf. 1986) and relied upon by the Examiner:

(1) the quantity of experimentation necessary,
(2) the amount of direction or guidance presented,
(3) the presence or absence of working examples,
(4) the nature of the invention,
(5) the state of the prior art,
(6) the relative skill of those in the art,
(7) the predictability or the unpredictability of the art, and
(8) the breadth of the claims.

Upon reviewing the facts related to the eight listed factors and determining that they supported a conclusion that undue experimentation was not required to practice the claimed invention in *In re Wands*, the court explained the basis for their finding at page 740 (1406):

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

Applicant's disclosure also provides considerable direction and guidance on how to practice their invention to the extent claimed. As stated by the Examiner, the most pertinent factors outlined above, with respect to the present invention are the scope of the claims, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to carry out the invention.

<u>The Amount of Direction or Guidance Provided</u>

As described above, the enablement requirement of 35 U.S.C. §112, first paragraph requires that the specification provide sufficient disclosure to permit one of skill in the art to practice the claimed invention without undue experimentation. Accordingly, given the claims of the present invention, the specification must teach one of skill in the art how to make a vaccine according to the invention, including a description of the cytokines and antigens to be included in the vaccine. The specification must also teach what types of cells may be used to produce the vaccine composition, and how to administer the vaccine to a mammal. Lastly, the specification must teach how one of skill in the art would determine whether a mammal to which the vaccine is administered, is vaccinated according to the invention. The specification teaches the following.

1. The specification teaches on pages 16-47, more than six different families of cytokines useful in the invention, including over 80 specifically referenced cytokine molecules which may be used in vaccine compositions of the invention.

2. The specification teaches at pages 68-71, that antigens useful in the methods of the invention include **viral antigens** including hepatitis viral antigens e.g., hepatitis A, B. and C, viral components such as hepatitis C viral RNA; influenza viral antigens such as hemagglutinin and neuraminidase and other influenza viral components; measles viral antigens such as the measles virus fusion protein and other measles virus components; rubella viral antigens such as proteins E1 and E2 and other rubella virus components; rotaviral antigens such as VP7sc and other rotaviral components; cytomegaloviral antigens such as envelope glycoprotein B and other cytomegaloviral antigen components; respiratory syncytial viral antigens such as the RSV fusion protein, the M2 protein and other respiratory syncytial viral antigen components; herpes simplex viral antigens such as immediate early proteins, glycoprotein D, and other herpes simplex viral antigen components; varicella zoster viral antigens such as gpI, gpII, and other varicella zoster viral antigen components; Japanese encephalitis viral antigens such as proteins E, M-E, M-E-NS 1, NS 1, NS 1 -NS2A, 80%E, and other Japanese encephalitis viral antigen components; rabies viral antigens such as rabies glycoprotein, rabies nucleoprotein and other rabies viral antigen components; **bacterial antigens**, including pertussis bacterial antigens such as pertussis toxin, filamentous hemagglutinin, pertactin, FIM2, FIM3, adenylate cyclase and other pertussis

bacterial antigen components; diptheria bacterial antigens such as diptheria toxin or toxoid and other diphtheria bacterial antigen components; tetanus bacterial antigens such as tetanus toxin or toxoid and other tetanus bacterial antigen components; streptococcal bacterial antigens such as M proteins and other streptococcal bacterial antigen components; gram- negative bacilli bacterial antigens such as lipopolysaccharides and other gram-negative bacterial antigen components; Mycobacterium tuberculosis bacterial antigens such as mycolic acid, heat shock protein 65 (HSP65), the 30kDa major secreted protein, antigen 85A and other mycobacterial antigen components; Helicobacter pylori bacterial antigen components; pneumococcal bacterial antigens such as pneumolysin, pneumococcal capsular polysaccharides and other pneumococcal bacterial antigen components; hemophilus influenza bacterial antigens such as capsular polysaccharides and other hemophilus influenza bacterial antigen components; anthrax bacterial antigens such as anthrax protective antigen and other anthrax bacterial antigen components; rickettsiae bacterial antigens such as romps and other rickettsiae bacterial antigen component; **fungal antigens** such as candida fungal antigen components; histoplasma fungal antigens such as heat shock protein 60 (HSP60) and other histoplasma fungal antigen components; cryptococcal fungal antigens such as capsular polysaccharides and other cryptococcal fungal antigen components; coccidiodes fungal antigens such as spherule antigens and other coccidiodes fungal antigen components; and tinea fungal antigens such as trichophytin and other coccidiodes fungal antigen components; **parasite antigens** such as plasmodium falciparum antigens such as merozoite surface antigens, sporozoite surface antigens, circumsporozoite antigens, gametocyte/gamete surface antigens, blood-stage antigen pf 1 55/RESA and other plasmodial antigen components; toxoplasma antigens such as SAG-1, p30 and other toxoplasma antigen components; schistosomae antigens such as glutathione-S-transferase, paramyosin, and other schistosomal antigen components; leishmania major and other leishmaniae antigens such as gp63, lipophosphoglycan and its associated protein and other leishmanial antigen components; and trypanosoma cruzi antigens such as the 75-77kDa antigen, the 56kDa antigen and other trypanosomal antigen components; and **tumor antigens** such as telomerase components; multidrug resistance proteins such as P-glycoprotein; MAGE-1, alpha fetoprotein, carcinoembryonic antigen, mutant p53, papillomavirus antigens, gangliosides or other carbohydrate-containing components of melanoma or other tumor cells.

3. The specification teaches at page 71 to 76, methods for expressing nucleic acid molecules encoding antigens of the invention in a host cell. The specification also teaches at page 78, lines 3-6 that a cell of the invention may already express a target antigen, and therefore need not be made to express the antigen.

4. The specification teaches at page 76-77, multiple cell types which may be used according to the invention to generate cytokine-coated cells.

5. The specification teaches at page 104-107, methods for administering the vaccine of the invention to a mammal, including methods for preparing pharmaceutical formulations, dosages, and routes of administration.

6. The specification teaches at page 82-89, **methods for determining whether an mammal has been vaccinated by a vaccine composition according to the invention**. Specifically, the specification teaches that vaccination of a mammal may be determined by assays for antigen-induced T cell proliferation, assays for lymphokine-dependent cell proliferation, [^{3}H]thymidine pulse and harvest of cell cultures, immuno-enzymatic assays for cytokines using NIP- and HRPO-labeled antibodies, measuring induction of *in vivo* antibody responses to protein/polysaccharide antigens, and assays using tumor rejection. With respect to determining vaccination based on tumor rejection, the specification teaches that if survival or tumor onset in animals to which have been administered a vaccine of the invention differs from that of a control animal, then immunomodulation has been achieved.

Thus, the specification provides more than ample guidance to one of skill in the art to practice the invention according to the full scope of the claims. The specification teaches how to utilize any cytokine according to the methods of the invention and methods for determining the effectiveness of the vaccine compositions of the invention. The individual methodologies, molecules, and molecular biological techniques described in the application for use in practicing the invention are routine in the art. Accordingly, given Applicant's teachings of the specific types of molecules to be used according to the invention, and the teachings of specific routine assays to determine whether a mammal is vaccinated by the method of the invention, provide

sufficient disclosure to permit one of skill in the art to practice the invention without undue experimentation.

The Examiner has defined a "vaccine" as "a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent". The Examiner asserts that the success of vaccination is to be judged by the extent or increase in the level of antigen-specific antibody. The Examiner also instructs Applicant that the second criterion for a vaccine is the ability to stimulate memory T cells. Accordingly, the Examiner asserts that the specification is not enabling because the specification does not provide information on the immunogenicity of any vaccine comprising any cytokine-coated cell comprising antigen or the ability of such to "protect or prevent from antigen-specific disease". Applicant respectfully disagrees with the Examiner.

Applicant submits that the present invention is set out by the claim as written, and that the terms used in the claims are to be defined by the Applicant, not the Examiner. As stated in the Manual of Patent Examining Procedure (MPEP) § 2111.02:

> Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998).

That is, terms which appear in the claims may be defined by Applicant as desired, provided that the definition does not a significant departure from what is accepted in the art. In the current rejection, the Examiner appears to be telling Applicant what the terms of the claims mean, instead of looking to the specification to determine the meaning given to the terms by Applicant. In particular, the Examiner asserts that the terms "vaccine" and/or "vaccinate" must mean the prevention or protection against a specific disease; it is this definition on which the Examiner has based much of the present enablement rejection. A reading of the specification, however, shows that Applicant has defined the term "vaccinate" as the modulation of an immune response to a

selected antigen (page 9, lines 21-22). More specifically, the specification defines "vaccinating" as the modulation of an immune response to a selected antigen such that "the response is between about 5 and 100%...more or less efficient, more or less rapid, greater or lesser in magnitude, and/or more or less easily induced" (page 9, line 26 – page 10, line 1). Moreover, as described above, Applicant has provided extensive teachings as to how one of skill in the art would determine the modulation of an immune response, including assaying for tumor rejection. The specification teaches on page 89, lines 12-19 that if survival or tumor onset in an animal to which has been administered a cytokine-coated cell of the invention differs from a control animal, then immunomodulation has occurred. More specifically, the specification teaches that if at least 10% of the animals in the test group survive 100% longer than the mean survival in the control group, the test is positive, or alternatively, if onset of tumors in 20% of the test animals is 50% later than mean onset in the control animals, the test is positive (i.e., animals are vaccinated). The examples provided in the specification teach that B16 melanoma cells mixed with either the engineered cytokine GM-CSF-GPI alone or the combination of GM-CSF-GPI and the engineered opsonin C3b alpha-GPI, when introduced back into the host organism, are capable of decreasing tumor formation, thus vaccinating the animal against the tumor cells. In addition, the Rule 132 Declaration filed with Applicant's response of February 28, 2003 clearly demonstrates that mice vaccinated with GM-CSF cytokine coated cells (fibrosarcoma cells) of the invention fall within the definition of "vaccinating" as described in the specification.

Applicant is not required to provide data demonstrating the ability of the vaccine compositions of the invention to protect or prevent from antigen-specific disease, or to be capable of generating an antibody response as asserted by the Examiner. While the generation of an antibody response is a step in a subset of immunological pathways, the present invention focuses on the targeting of an antigen bearing cell to an antigen presenting cell. That is, the present invention is based on the discovery that the admixture of a cell bearing a given antigen with an exogenous cytokine, where the cytokine becomes stably associated with the cell surface, results in a vaccine composition which is capable of effectively targeting the antigen to an antigen presenting cell. Applicant is therefore only required to provide sufficient teachings to permit one of skill in the art to reproduce the present invention as claimed (including the meaning given to terms in the claims by Applicant), without undue experimentation; that is, how

to make and administer a vaccine composition of the invention which is capable of vaccinating an animal as defined by the specification. Applicant has taught how to make a vaccine composition of the invention; has taught the components of such a vaccine composition; has taught the administration of such a vaccine composition; have taught how one of skill in the art would determine whether a mammal had been vaccinated or not; and have provided data which demonstrates that, as evaluated by one of the assays taught in the specification (i.e., protection against tumors) that the vaccine compositions of the invention are capable of vaccinating a mammal.

The Quantity of Experimentation Necessary

When commenting on the amount of experimentation constituting an acceptable quantity of experimentation, the Wands Court, quoting *In re Jackson*, 217 U.S.P.Q.2d 807, stated at page 737 that:

> . . .a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Thus, the critical issue for this factor is not the quantity of experimentation required to practice the invention as claimed, but the type of experimentation required and the amount of guidance provided to the ordinarily skilled artisan. In the instant case, the specification provides extensive teachings regarding the invention and the methods of practicing it, as described above. In particular, Applicant has taught how to make the vaccine compositions of the invention, how to use the vaccine compositions of the invention, and how to determine if such a composition is effective in vaccinating a mammal against a selected antigen.

The Examiner asserts that one of skill in the art would have to practice undue experimentation to reproduce the invention, but does not support this statement with objective evidence. **To reject the claims for lack of enablement, the Examiner must make specific findings of fact, supported by the evidence, as to why one of skill in the art would not be**

able to practice the invention, given the extensive teachings provided by Applicant, without undue experimentation (MPEP 2164.04). In addition, the Examiner is required to provide specific technical reasons why undue experimentation would be required to practice the invention (Id.). Applicant submits that, other than stating that undue experimentation would be required to practice the invention, the Examiner has not pointed out any technical, factual reasons why this would be the case.

The Examiner repeatedly asserts that the specification is not enabling for the administration of *any* vaccine comprising *any* cytokine coated cell and *any* antigen. Applicant submits that the specification provides sufficient teaching to permit one of skill in the art to generate a vaccine composition comensurate with the scope of the claims as written. The invention utilizes the multiplicity of antigens expressed by the cytokine coated cell to provide the immune system with all of the antigens in the cytokine coated cell against which to mount an immune response. Applicant submits that the specification provides significant guidance to permit one of skill in the art to practice the invention as claimed without undue experimentation. As indicated above, some experimentation, even "a considerable amount" of experimentation is permitted provided that the specification provides sufficient guidance. The present specification teaches how to make and use the vaccine compositions of the invention commensurate with the scope of the claims, and further teaches how one of skill in the art would determine whether a mammal has been vaccinated according to the invention. Applicant therefore submits that no undue experimentation is required and request that the rejection be withdrawn.

The Presence or Absence of Working Examples

Applicant submits that the enablement of the claims of the invention is based on the specification as a whole, and does not turn on whether Applicant discloses a working example. The MPEP is clear that Applicant need not have actually reduced the invention to practice prior to filing (MPEP 2164.02). Citing *Gould v Quigg*, 822 F.2d 1074, the MPEP notes that the mere fact that something has not been previously done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. An example may be either "working" or "prophetic".

Applicant submits that the specification includes fourteen (14) examples which are both working and prophetic, describing the construction of vaccine compositions of the invention (working), and the use of such compositions to vaccinate mammals (prophetic), including dosage and mode of administration. Moreover, **Applicant has filed with their previous response of February 28, 2003, a Rule 132 declaration by Dr. Andrew Segal which provides data to show that the vaccine compositions of the present invention are effective in vaccinating a mammal to which they are administered.** Accordingly, Applicant submits that the specification provides an enabling disclosure which is verified by the experimental data provided in the Rule 132 declaration.

The Predictability of the Art

The Examiner cites several references in an apparent effort to demonstrate that the state of the art surrounding Applicant's invention is unpredictable, and that Applicant's disclosure is therefore insufficient. Applicant respectfully disagrees with the Examiner.

The Examiner has cited several sources, the majority of which were published at least three years prior to Applicant's earliest filing date, and were therefore out of date as of Applicant's filing date, to support the position that the claimed invention is unpredictable, and therefore not enabled. Applicant respectfully submits, however, that the Examiner has mischaracterized several of the references, taking the quoted passages out of context.

The Examiner asserts that it is "well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity". The Examiner asserts that Ellis (Chapter 29 of Vaccines, published seven years before Applicant's filing date) "exemplifies this problem" in the recitation that "The key to the problem is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies...and thus protect the host against attack by the pathogen". Applicant submits that the quoted phrase is used in the context of describing the development of recombinant DNA based vaccine, and uses the term "problem" to refer to a scientific issue, rather than an aspect of the technology which is "problematic". In fact, Ellis goes on to teach that, once identified, the gene encoding the protein is placed in a host cell resulting in the

synthesis of large amounts of the immunogenic protein. Ellis then describes the great success that this technique has achieved. Specifically, Ellis teaches that such pathogenic antigen-based vaccine compositions have been used to produce a "safe and effective" vaccine against hepatitis B virus (HBV). Clearly, Ellis is not teaching, as the Examiner asserts, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Regardless of the forgoing discussion, Applicant submits that the "problem" asserted by the examiner is irrelevant to the practice of the present invention. The present invention is designed to target an *antigen bearing cell* to a leukocyte by attaching exogenous cytokine molecules to the cell. Accordingly, the invention does not require that a specific antigen be identified; indeed, the invention provides a method by which every antigen in the cell is targeted to immune cells, and thus offered to the host's immune system. Thus, there is no "problem" of antigen selection to overcome. The invention provides the immune system with all the antigens present in the cytokine coated cell against which to mount an immune response and eradicate the antigen bearing cells; this occurs without the need for the practitioner to know precisely what antigen present in the cytokine coated cell will trigger the immune response.

The Examiner also cites Chandrasheker et al. (U.S. Pat. No. 6,248,329), asserting that the '329 patent teaches that it is understood in the art that the ability of antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from a specific disease, "associated with the antigen". Applicant submits, however, that this teaching is provided in the context of parasitic helminths. Specifically, the Examiner has omitted the final phrase of the relevant passage of the '329 patent which recites "associated with the antigen, *particularly in the case of parasitic helminths*". Thus, the 'unpredictability' purported to be taught by the '329 patent is limited to stimulation of an immune response with antigen from one particular organism, in an attempt to stimulate immunity against one particular type of infection. In addition, the '329 states that "the ability of an antigen to stimulate antibody production does not *necessarily* correlate with the ability of the antigen to stimulate an immune response", which means that it is also likely that there is a correlation between antigen and an antibody response. Moreover, Applicant submits that the specification need not enable each and every potential embodiment of the invention (See, eg., *Atlas Powder Co. v. E.I. du Pont de Nemours &Co*, 750 F.2d 1596 (Fed. Cir. 1984) (holding that

the presence of inoperative embodiments does not necessarily render a claim nonenabled)), provided that the specification provides sufficient guidance to permit one of skill in the art to practice the invention without undue experimentation. Thus, even if one of skill in the art were to encounter difficulty in vaccinating a mammal against a parasitic helminth antigen, the specification provides sufficient guidance to permit one of skill in the art to determine whether such an embodiment would be operative or not, and thus the specification, as a whole, is enabling for the full breadth of the claimed invention. Moreover, as described above, the invention provides a method for providing all of the antigens in a cytokine coated cell of the invention to the immune system, against which the immune system can mount an appropriate response to vaccinate the animal.

The Examiner also cites Spitler (Cancer Biotherapy, published three years prior to Applicant's filing date), as speculating on the negative view an oncologist or venture capitalist would have of cancer vaccines if anyone were to bother to ask them. What the Examiner fails to point out, however, is that Spitler goes on to teach that "cancer vaccines have finally reached the stage in technological development where commercial development can be envisioned" (page 2, first full paragraph). Spitler notes that developing technology has permitted scientists to identify and characterize tumor associated antigens, determine their tissue distribution, and produce virtually unlimited quantities of pure antigens for use in vaccine development (Id.). Interestingly, in contrast to the Examiner's overarching assertion that vaccination against a particular antigen is insufficient to modulate disease, Spitler states that "[A]lmost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy", and that "[I]nvestigators who have reported clinical successes with vaccine therapy in large series of patients include..." (citing Berd et al., *Ann NY Acad. Sci.* 1993, 690: 147; Bystryn, *Ann NY Acad Sci*, 1993, 690:190; Hersey et al., *Cancer Immunol Immunother*, 1986, 22:221; Mitchell et al., *Ann NY Acad Sci*, 1993, 153:666; Morto et al., *Ann NY Acad Sci*, 1993, 690:120; Seigler et al., *J. Biol Resp Modifiers* 1989, 1-16; Wallack et al., *Cancer*, 1986, 57:649). In contrast to the opening speculation as to the opinion of oncologists and venture capitalists, Spitler concludes by declaring, "[T]he decade of the vaccines may finally have arrived!"

The Examiner lastly cites Ezzell (NIH Research); asserting that Ezzell teaches that "tumor cells simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes". Applicant submits that the present invention does not rely "simply" on the display of a unique antigen on the surface of a cell for recognition by a T cell. In contrast the present invention provides a cytokine coated cell comprising the selected antigen and an exogenous cytokine. Without being bound to one particular theory, the present invention is based, in part on the discovery that a cytokine on the surface of an antigen bearing cell will interact with a cell surface receptor on a leukocyte (including APCs such as dendritic cells), thus promoting engulfment and presentation of the antigen by the leukocyte. Thus, the present invention goes beyond the mere antigen expression which is disfavored by Ezzell, and provides an effective method (demonstrated by Applicant's teachings combined with the Dr. Segal's Rule 132 declaration) of vaccinating a mammal against a selected antigen.

The Examiner asserts that Ezzell teaches that "no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent...later growth". Ezzell continues to say, however, that most cancer immunologists are still looking for more effective ways to prompt cancer patients immune systems to reject tumors. Applicant submits that the present invention provides just that; a more effective way to prompt tumor rejection and vaccination of a mammal against a selected antigen. Moreover, regardless of the outdated pessimism documented by Ezzell, Applicant has demonstrated that *the claimed invention works*, and is capable of vaccinating a mammal to a selected antigen.

Accordingly, Applicant respectfully submits that the Examiner's assertion that the state of the art supports the conclusion that the present invention is unpredictable and/or inoperative is incorrect. Applicant submits that the specification provides extensive teaching as to the manner of making and using the claimed invention, and plural methods for determining whether an animal is vaccinated according to the invention, such that one of skill in the art could readily adapt the methods to a particular selected antigen of interest, and predict generally what the outcome would be.

Summary

In summary, a reasonable consideration of the factors relating to whether undue experimentation would be required to practice the claimed invention must lead to a conclusion that the claims are fully enabled. The quantity of experimentation required to perform any particular embodiment is not large, and is further offset by the teachings and guidance provided in the application, the familiarity of the ordinarily skilled artisan with assay adaptation and the amount of information available in the art. The application provides a great deal of direction and guidance and includes many examples, both prophetic and working. The skill in the art is high, and a great deal of information is available in the prior art. Accordingly, Applicant requests that the rejection for lack of enablement be reconsidered and withdrawn.

Rejection of Claims 17-20 and 22-25 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 17-20 and 22-25 as being indefinite as being dependent on cancelled claims 9, 10, 15, and 21. Applicant submits that the claims have been amended herein so as to remove the dependency on the cancelled claims.

The Examiner has rejected claim 25 as being indefinite in the recitation of "cytokine is extremely bioactive, natively bioactive, or suprabioactive". The Examiner asserts that the characteristics and metes and bounds of these terms are ambiguous and indefinite. Applicant respectfully disagrees.

Applicant submits that each of "extremely bioactive", "natively bioactive" and "suprabioactive" are clearly defined on page 51, lines 6-17 of the specification. Specifically, the specification teaches:

> According to the invention, if a non-naturally occurring cytokine gives a readout in a bioactivity assay that is at least 50% but not more than 69% (to the nearest 1%) of the readout yielded by an equimolar amount of a naturally occurring cytokine (the latter giving a positive result in the assay), then the non-naturally occurring cytokine is "**extremely bioactive**". According to the invention, if a non-naturally occurring cytokine gives a readout in a bioactivity assay that is at least 70% but not more than 100% (to the nearest 1%) of the readout yielded by an equimolar amount of a naturally occurring cytokine (the latter giving a positive

> result in the assay), then the non-naturally occurring cytokine is "**natively bioactive**". According to the invention, if a non-naturally occurring cytokine gives a readout in a bioactivity assay that is greater than 100% of the readout yielded by an equimolar amount of a naturally occurring cytokine (the latter giving a positive result in the assay), then the non-naturally occurring cytokine is "**suprabioactive**". (emphasis added)

Accordingly, Applicant submits that the terms are clearly defined in the specification, and thus are not ambiguous or indefinite. Applicant requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 13, 14, 17-19, and 22-25 Under 35 U.S.C. §102(e)

The Examiner has rejected claims 1, 2, 13, 14, 17-19, and 22-25 under 35 U.S.C. §102(e) as being anticipated by Hiserodt et al. (U.S. Pat. No. 6,277,368). The Examiner asserts that Hiserodt teaches vaccinating a mammal to a selected antigen by administering cytokine *secreting* cells. The Examiner further asserts that Hiserodt teaches that the cytokines secreted by the cells are exogenous to primary tumor cells, and further that it is possible to engineer membrane-bound forms of the cytokine, and that it is preferable that the cytokine be attached to the membrane. Applicant respectfully disagrees with the Examiner.

Applicant submits that the present claims recite a method of vaccinating a mammal against a selected antigen by administering a vaccine composition comprising a cytokine coated cell comprising the selected antigen and wherein the cytokine is exogenous to the cytokine coated cell. The specification defines "exogenous" at page 10, lines 28-29, as a cytokine "which is introduced from or produced outside the cell". Applicant submits that Hiserodt does not teach vaccine compositions comprising a cytokine coated cell comprising an exogenous cytokine.

The Examiner asserts that Hiserodt teaches cytokine secreting cells. The Examiner further asserts that Hiserodt teaches that the cytokines secreted by the cytokine secreting cells are exogenous to primary tumor cells (col. 7, lines 25-40). Applicant disagrees. By definition, a cytokine *secreting* cell is not a cell in which the cytokine is exogenous to the cell; a cytokine secreting cell is one in which the cytokine is an endogenous cytokine. In other words, a cytokine secreting cell necessarily produces the cytokine within the cell; the cytokine of a cytokine

secreting cell is not introduced from or produced outside the cell. Thus, the passage cited by the Examiner teaches precisely that, in marked contrast to the Applicant's invention, the cytokine of Hiserodt is **not** exogenous to the cytokine secreting cell. At line 27-35, Hiserodt teaches that "the cytokine is primarily secreted by the cell", and that in other embodiments the "cytokine is produced by the cell as a transmembrane protein". This teaching indicates that the cytokines of Hiserodt are produced by the cell, in contrast to the requirements of the present claims, i.e. that the cytokine be exogenous to the cell, i.e. that it *not* be produced by the cell.

The Examiner also asserts that Hiserodt teaches that where a particular cytokine has a potent immunostimulatory activity but does not naturally occur in a membrane-bound form, that it is possible to [engineer] a membrane-bound form of the cytokine (citing col. 16, lines 50-65). Hiserodt teaches that a membrane bound form of the cytokine may be produced by generating a fusion protein between the cytokine and a transmembrane region, and that, in order to use such a cytokine, "cells are genetically altered with a vector comprising a cytokine encoding region and a transmembrane region in the same open reading frame". This is the sole method taught by Hiserodt for attaching a cytokine to a cell. Such cytokines are thus, again, not exogenous to the cell as required by Applicant's claims. Furthermore, the use of exogenous cell-binding cytokines has numerous practical, scientific, and potential safety advantages over the genetic modification of cells to produce endogenous, transmembrane cytokines.

Accordingly, Applicant submits that Hiserodt does not anticipate the claimed invention, and request that the rejection be reconsidered and withdrawn.

Rejection of Claims 3-8 and 20 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3-8 and 20 under 35 U.S.C. §103 as being obvious over Hiserodt in view of a "Known fact" disclosed in Applicant's specification on pages 52-54 and 66-68. The Examiner asserts that Hiserodt's teachings are deficient with respect to claims 3-8 and 20 in that Hiserodt does not teach the specific types of engineered cytokine or specific opsonin-enhanced cells as recited in these claims. The Examiner asserts, however, that the "Known fact" disclosed in the specification teaches that it is conventional and within the skill of the art to produce (i) an opsonin-enhanced cell, wherein the opsonin of the cell is mannose

binding protein or alpha' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching a lipid to the cytokine to permit a complex to become stably associated with the cell membrane. Applicant respectfully disagrees with the Examiner.

For the reasons described below, Applicant respectfully submits that the Examiner has failed to establish a prima facie case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Applicant submits that there is no motivation to combine the teachings suggested by the Examiner. Applicant submits that the disclosure in the specification (the "known fact" asserted by the Examiner) that the technology existed to link a lipid moiety to a cytokine molecule does not equate to a teaching that such a modification of a cytokine is obvious. The level of skill in the art (e.g., the technique for modifying a cytokine to include a cell membrane binding moiety) cannot be relied upon to provide the suggestion to combine references (*Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999)). The "Known fact" referred to by the Examiner, that such an engineered cytokine could be used according to the methods of the invention to vaccinate a mammal against a selected antigen, and that the vaccine composition may be combined with an opsonin is a teaching which is unique to the present specification. The combination of a cytokine coated cell and an opsonin as claimed in the invention is not a "known fact". As the Examiner is no doubt aware, taking the teachings of the present invention relating to the claimed method and attempting to fill in the gaps in the prior art with such teachings amounts to hindsight reconstruction of the invention, and is not permitted.

The law is clear that "[i]t is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention...The references themselves must provide some teaching whereby the Applicant's combination would have been obvious." (*In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991)). Applicant submits that there is no motivation in the teachings of Hiserodt to motivate one of skill in the art to make the claimed invention, thus rendering the invention obvious. Hiserodt teaches only *endogenous* expression of cytokines comprising a transmembrane amino acid sequence, and does not teach a vaccine composition comprising a cytokine coated cell, wherein the cytokine is exogenous to the cell. The motivation to combine the references cited by the Examiner is gleaned only from Applicant's own disclosure of the invention, and is thus an impermissible hindsight reconstruction of the claimed invention (*In re McLaughlin*, 433 F.2d 1392 (CCPA 1971)). Moreover, Applicant submits that the present specification actually teaches away from the combination suggested by the Examiner. Page 15, lines 8-12 teaches that the present invention provides unexpected results, in that the prior art teaches that the C-terminus of cytokines, such as GM-CSFis important for interaction with a cognate receptor, and that GPI moieties attach to the C-terminus of proteins. Thus, the expectation of one of skill in the art would be that the attachment of aGPI moiety to the C-terminus of a cytokine would interfere with the binding of the cytokine to its receptor. Accordingly, one of skill in the art would not be motivated to modify the teachings of Hiserodt to include a GPI-linked cytokine because the state of the art described in Applicant's specification suggests that such a combination would not be successful. Applicant submits that the state of the art summarized in Applicant's disclosure teaches away from the suggested combination. In addition, Applicant's invention has a distinct advantage over the teachings of Hiserodt. As taught in Applicant's specification on page 15, lines 18-20, Applicant's invention is advantageous over the teachings of Hiserodt in that the cytokine-coated cells of the invention may be prepared more quickly and with less labor than cells transduced with a heterologous cytokine gene as taught by Hiserodt. The methods of the present invention do not require the introduction of a foreign gene into the vaccine cell. It is known in the art that primary tumor cells are difficult to transduce (although the present invention is not limited to primary tumor cells). The present invention provides a way to attach a cytokine to a cell without performing the expensive, time consuming, and difficult task of expressing the cytokine from the vaccine cell.

With respect to the Examiner's assertion that one of skill in the art would have been motivated to include in the vaccine composition, an opsonin-enhanced cell, Applicant submits that this rejection is entirely improper. There is no teaching whatsoever in Hiserodt of the use of an opsonin-enhanced cell. The only teaching of an opsonin-enhanced cell combined with a cytokine coated cell, and the theory that such a component of a vaccine composition may lead to more efficient binding, engulfment, and internalization of an antigen, is found in Applicant's disclosure. This is a clear instance of hindsight reconstruction of Applicant's invention. The Examiner is essentially saying that Applicant's description of their own invention makes their own invention obvious. If this were to be the case, then every patent specification would be 103 prior art against itself, as every specification must describe the invention which is supports. Applicant respectfully submits that this type of circular logic is not a proper basis for a rejection under §103.

Applicant submits further that the inclusion of an opsonin-enhanced cell provides a clear advantage over the teachings of Hiserodt, an advantage which is not even contemplated in Hiserodt. The present specification teaches that the inclusion of an opsonin-enhanced cell may provide a "link or coupling agent...between the antigen and the APC", thus allowing more "efficient binding, engulfment, and internalization of the antigen-containing cell" (page 12, lines 14-16). Thus, the presence of an opsonin-enhanced cell in the present invention provides a vaccine composition which is distinctly advantageous over the composition taught by Hiserodt (That is, a composition which lacks an opsonin-enhanced cell and utilizes an endogenous cytokine), in that the presence of an opsonin-enhanced cell according to the present invention, increases the functionality of the already effective cytokine-coated cell vaccine composition of the invention. This advantage is unique to Applicant's invention and is not even suggested by Hiserodt. Thus, Applicant asserts that the present invention may not be rendered obvious by a technological advancement which is solely the inventive effort of the Applicant and which is not taught or suggested in the combination of prior art cited by the Examiner.

Applicant therefore submits that the present invention is not obvious over Hiserodt in view of Applicant's own disclosure, and request that the rejection be reconsidered and withdrawn.

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicant respectfully requests the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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